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Preoperative imaging for colorectal liver metastases: a nationwide population-based study

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Background: **In patients with colorectal liver metastases (CRLM) preoperative imaging may include contrast-enhanced (ce) MRI and [^{18}F]fluorodeoxyglucose (^{18}F-FDG) PET–CT. This study assessed trends and variation between hospitals and oncological networks in the use of preoperative imaging in the Netherlands.**

Methods: **Data for all patients who underwent liver resection for CRLM in the Netherlands between 2014 and 2018 were retrieved from a nationwide auditing database. Multivariable logistic regression analysis was used to assess use of ceMRI, ^{18}F-FDG PET–CT and combined ceMRI and ^{18}F-FDG PET–CT, and trends in preoperative imaging and hospital and oncological network variation.**

Results: **A total of 4510 patients were included, of whom 1562 had ceMRI, 872 had ^{18}F-FDG PET–CT, and 1293 had combined ceMRI and ^{18}F-FDG PET–CT. Use of ceMRI increased over time (from 9·6 to 26·2 per cent; $P < 0·001$), use of ^{18}F-FDG PET–CT decreased (from 28·6 to 6·0 per cent; $P < 0·001$), and use of both ceMRI and ^{18}F-FDG PET–CT 16·9 per cent) remained stable. Unadjusted variation in the use of ceMRI, ^{18}F-FDG PET–CT, and combined ceMRI and ^{18}F-FDG PET–CT ranged from 5·6 to 100 per cent between hospitals. After case-mix correction, hospital and oncological network variation was found for all imaging modalities.**

Discussion: **Significant variation exists concerning the use of preoperative imaging for CRLM between hospitals and oncological networks in the Netherlands. The use of MRI is increasing, whereas that of ^{18}F-FDG PET–CT is decreasing.**

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Introduction

Colorectal liver metastases (CRLM) are the leading indication for liver surgery in the Netherlands, accounting for approximately 1000 liver resections each year[1].

Current multidisciplinary management of CRLM by surgeons, interventional radiologists, radiation therapists and oncologists demands detailed preoperative knowledge consisting of anatomical location in relation to vascular structures, number and size of CRLM, and individual patients' risks and preferences[2,3]. Increasingly used options include contrast-enhanced (ce) MRI and [^{18}F]fluorodeoxyglucose (^{18}F-FDG) PET–CT[4–6]. ceMRI

Table 1 Baseline characteristics for preoperative imaging in patients diagnosed with colorectal liver metastases between 2014 and 2018 in the Netherlands

	No additional imaging ($n = 783$)	MRI ($n = 1562$)	PET–CT ($n = 872$)	MRI + PET–CT ($n = 1293$)	P‡
Age (years)					0·038
≤ 70	496 (63·5)	1001 (64·2)	520 (59·7)	867 (67·2)	
> 70	285 (36·5)	559 (35·8)	351 (40·3)	424 (32·8)	
Missing	2	2	1	2	
Sex					0·078
M	468 (59·8)	1012 (64·8)	555 (63·6)	796 (61·6)	
F	315 (40·2)	550 (35·2)	317 (36·4)	497 (38·4)	
Charlson Co-morbidity Index					< 0·001
0–1	593 (76·7)	1186 (77·1)	598 (69·0)	955 (74·7)	
≥ 2	180 (23·3)	352 (22·9)	269 (31·0)	324 (25·3)	
Missing	10	24	5	14	
BMI (kg/m^2)*	26·1(4·4)	26·3(4·3)	26·1(4·4)	26·5(4·4)	0·124§
ASA grade					0·032
I–II	606 (77·9)	1271 (81·6)	654 (79·3)	1058 (82·6)	
≥ III	172 (22·1)	286 (18·4)	171 (20·7)	223 (17·4)	
Missing	5	5	47	12	
Previous liver resection					0·002
No	615 (79·8)	1303 (84·6)	681 (79·0)	1063 (82·7)	
Yes	156 (20·2)	238 (15·4)	181 (21·0)	222 (17·3)	
Missing	12	21	10	8	
History of liver disease†					0·145
No	758 (98·8)	1499 (98·1)	839 (98·5)	1225 (99·1)	
Yes	9 (1·2)	29 (1·9)	13 (1·5)	11 (0·9)	
Missing	16	34	20	57	
History of preoperative chemotherapy					< 0·001
No	457 (64·5)	1004 (70·1)	581 (75·0)	800 (68·6)	
Yes	252 (35·5)	429 (29·9)	194 (25·0)	367 (31·4)	
Missing	74	129	97	126	
No. of lesions					< 0·001
1	353 (47·5)	617 (40·5)	440 (52·1)	515 (40·8)	
2	153 (20·6)	339 (22·3)	199 (23·6)	260 (20·6)	
3	91 (12·2)	160 (10·5)	95 (11·3)	157 (12·5)	
4	52 (7·0)	112 (7·4)	41 (4·9)	110 (8·7)	
5	28 (3·8)	81 (5·3)	24 (2·8)	57 (4·5)	
> 5	66 (8·9)	214 (14·1)	45 (5·3)	162 (12·8)	
Missing	40	39	28	32	
Maximum diameter of largest CRLM (mm)					< 0·001
< 20	169 (26·2)	514 (35·8)	180 (24·7)	369 (31·3)	
20–34	232 (36·0)	544 (37·9)	297 (40·8)	437 (37·1)	
35–54	137 (21·3)	239 (16·7)	157 (21·6)	231 (19·6)	
≥ 55	106 (16·5)	137 (9·6)	94 (12·9)	141 (12·0)	
Missing	139	128	144	115	
Location of primary tumour					< 0·001
Colon	527 (67·5)	974 (62·5)	614 (70·4)	793 (61·3)	
Rectum	254 (32·5)	584 (37·5)	258 (29·6)	500 (38·7)	
Missing	2	4	0	0	
Nodal status of primary tumour					0·109
pN0	194 (35·6)	405 (37·0)	281 (41·4)	366 (37·3)	
pN1	206 (37·8)	406 (37·1)	233 (34·3)	349 (35·5)	
pN2	145 (26·6)	284 (25·9)	165 (24·3)	267 (27·2)	
Unknown	238	467	193	311	

Table 1 Continued

	No additional imaging (*n* = 783)	MRI (*n* = 1562)	PET–CT (*n* = 872)	MRI + PET–CT (*n* = 1293)	*P*‡
Type of metastases					< 0·001
Metachronous	390 (50·4)	723 (46·6)	552 (63·9)	697 (54·6)	
Synchronous	384 (49·6)	827 (53·4)	312 (36·1)	580 (45·4)	
Missing	9	12	8	16	
Extrahepatic disease					< 0·001
No	628 (91·1)	1383 (93.8)	702 (88.5)	1110 (91.1)	
Yes	61 (8.9)	92 (6.2)	91 (11.5)	109 (8.9)	
Missing	94	87	79	74	
Type of hospital					< 0·001
Regional	350 (44·7)	928 (59·4)	499 (57·2)	713 (55·1)	
Tertiary referral centre	433 (55·3)	634 (40·6)	373 (42·8)	580 (44·9)	
Year of surgery					< 0·001
2014	178 (22·7)	150 (9·6)	249 (28·6)	194 (15·0)	
2015	142 (18·1)	250 (16·0)	219 (25·1)	273 (21·1)	
2016	155 (19·8)	340 (21·8)	224 (25·7)	289 (22·4)	
2017	150 (19·2)	413 (26·4)	128 (14·7)	318 (24·6)	
2018	158 (20·2)	409 (26·2)	52 (6·0)	219 (16·9)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis. CRLM, colorectal liver metastases. ‡χ^2 test or Fisher's exact test, except §independent two-samples *t* test.

has been suggested to have a significant advantage over CT in detecting additional (small) liver metastases, in particular those of subcapsular or peribiliary origin[4,7–11]. The oncological advantage of preoperative ^{18}F-FDG PET–CT to assess CRLM is doubtful[12], although this imaging method seems to have an advantage in identifying extrahepatic metastases of colorectal cancer[13]. Some authors[14,15] propose using ^{18}F-FDG PET–CT during follow-up to assess intrahepatic and extrahepatic metastases. Several European countries have preoperative imaging guidelines that contain advice regarding the use of both ceMRI and ^{18}F-FDG PET–CT[16]. Guidelines in the UK[17,18] and Japan[19], as well as the European Society for Medical Oncology consensus guideline on metastatic colorectal cancer[20], point out that ceMRI and ^{18}F-FDG PET–CT can be performed in the preoperative work-up. However, these guidelines indicate that more research is needed to address the added value of preoperative imaging in patients with CRLM.

The Dutch guidelines[21] in dicate that, at baseline, CT should be performed to assess the presence of CRLM[22]. If treatment is considered, ceMRI can be performed to detect lesions smaller than 10 mm. The guideline further states that ^{18}F-FDG PET–CT should not be performed as part of preoperative work-up, but is indicated only when extrahepatic metastases are suspected.

The aims of the present study were to provide a population-based overview of factors associated with the use of different types of preoperative imaging modality, in patients with colorectal liver metastases, to report on trends over the years, and to assess variation between hospitals and oncological networks in the Netherlands.

Methods

This was a population-based nationwide cohort study performed in the Netherlands with data from the Dutch Hepato-Biliary Audit (DHBA)[23]. The Netherlands is a western European country with approximately 17 million inhabitants living on 33 883 square kilometres[24]. Healthcare is organized in 71 hospitals, including seven university hospitals and one comprehensive cancer centre[23,25]. Twenty-five hospitals perform liver surgery. A national minimum annual centre volume of 20 liver resections and infrastructural requirements (24/7 availability of an interventional radiologist) have led to the centralization of liver surgery[26]. Hospitals performing liver surgery in the Netherlands have been obliged to register liver resections in the DHBA since 2013. Detailed information on patient and disease characteristics, as well as diagnostic and treatment information, has been collected from 2013 onwards. Information regarding the formation and content of the DHBA has been described previously[23]. Data verification provided insight into the completeness and accuracy of the DHBA[27]. During this process, data in the DHBA were

Table 2 Association model of patient and tumour factors with the use of preoperative contrast-enhanced MRI in patients with colorectal liver metastases in the Netherlands, 2014–2018

	No. of patients (n = 4510)	Univariable analysis*		Multivariable analysis*	
		Odds ratio	*P*	Adjusted odds ratio	*P*
Age (years)			0·015		0·632
≤50	315	1·00 (reference)		1·00 (reference)	
50–64	1543	0·93 (0·72, 1·21)	0·603	0·96 (0·50, 1·96)	0·762
65–79	2331	0·81 (0·63, 1·04)	0·097	0·88 (0·71, 1·28)	0·383
≥80	314	0·67 (0·48, 0·93)	0·016	0·86 (0·66, 1·17)	0·418
Missing†	7				
Sex			0·310		
M	2831	1·00 (reference)			
F	1679	0·94 (0·83, 1·06)			
Charlson Co-morbidity Index			0·012		0·753
0–1	3332	1·00 (reference)		1·00 (reference)	
≥2	1125	0·84 (0·73, 0·96)		0·98 (0·83, 1·14)	
Missing†	53				
BMI		1·02 (1·00, 1·04)	0·023	1·02 (1·01, 1·04)	0·014
ASA grade			0·005		0·001
I–II	3589	1·00 (reference)		1·00 (reference)	
≥III	852	0·80 (0·69, 0·94)		0·74 (0·62, 0·88)	
Missing†	69				
History of liver disease‡			0·811		
No	4321	1·00 (reference)			
Yes	62	1·07 (0·64, 1·83)			
Missing†	127				
History of liver resection			<0·001		0·006
No	3662	1·00 (reference)		1·00 (reference)	
Yes	797	0·75 (0·64, 0·87)		0·79 (0·66, 0·94)	
Missing†	51				
History of preoperative chemotherapy			0·708		
No	2842	1·00 (reference)			
Yes	1242	1·03 (0·89, 1·18)			
Missing†	426				
No. of CRLM			<0·001		<0·001
1	1925	1·00 (reference)		1·00 (reference)	
2	951	1·19 (1·02, 1·40)	0·031	1·19 (1·00, 1·42)	0·051
3	503	1·19 (0·98, 1·46)	0·086	1·28 (1·02, 1·60)	0·047
4	315	1·67 (1·30, 2·17)	<0·001	1·71 (1·29, 2·27)	0·001
5	190	1·86 (1·34, 2·61)	<0·001	1·86 (1·29, 2·69)	0·002
>5	487	2·37 (1·89, 3·00)	<0·001	2·45 (1·89, 3·17)	<0·001
Missing†	139				
Maximum diameter of largest CRLM (mm)			<0·001		<0·001
<20	1232	1·00 (reference)		1·00 (reference)	
20–34	1510	0·73 (0·62, 0·86)	<0·001	0·72 (0·61, 0·87)	<0·001
35–54	764	0·63 (0·52, 0·77)	<0·001	0·66 (0·53, 0·81)	<0·001
≥55	478	0·55 (0·44, 0·69)	<0·001	0·56 (0·44, 0·72)	<0·001
Missing	526	0·34 (0·27, 0·42)	<0·001	0·32 (0·25, 0·40)	<0·001
Bilobar disease			0·716		
No	2423	1·00 (reference)			
Yes	2043	1·02 (0·91, 1·16)			
Missing†	44				

Table 2 Continued

	No. of patients (n = 4510)	Univariable analysis*		Multivariable analysis*	
		Odds ratio	*P*	Adjusted odds ratio	*P*
Location of primary tumour			< 0·001		< 0·001
Colon	2908	1·00 (reference)		1·00 (reference)	
Rectal	1596	1·37 (1·20, 1·56)		1·44 (1·25, 1·67)	
Missing†	6				
Nodal stage of primary tumour			0·607		
pN0	1246	1·00 (reference)			
pN1	1194	1·06 (0·90, 1·25)	0·489		
pN2	861	1·10 (0·91, 1·31)	0·323		
Missing	1209	1·11 (0·94, 1·31)	0·204		
Type of metastases			< 0·001		0·012
Metachronous	2362	1·00 (reference)		1·00 (reference)	
Synchronous	2103	1·34 (1·19, 1·52)		1·22 (1·05, 1·41)	
Missing†	45				
Extrahepatic metastases			< 0·001		0·003
No	3823	1·00 (reference)		1·00 (reference)	
Yes	566	0·66 (0·56, 0·80)		0·74 (0·60, 0·90)	
Missing	121				
Type of hospital			< 0·001		< 0·001
Regional	2490	1·00 (reference)		1·00 (reference)	
Tertiary referral centre§	2020	0·78 (0·69, 0·88)		0·79 (0·66, 0·89)	

Values in parentheses are 95 per cent confidence intervals. *Multilevel logistic regression model with individuals nested for year of surgery. †Missing values not included in analyses because of relatively small group. ‡Liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis. §Defined as hospitals with highest expertise on oncological surgery.

compared with those in the Dutch Cancer Registry. The completeness of data retrieved from 2015 was 97 per cent[23].

Patient selection

All consecutive patients who underwent liver resection for CRLM between 1 January 2014 and 31 December 2018, and were registered in the DHBA before 22 March 2019, were included in the study. Patients who had ablation of CRLM alone were not included in the study as registration of such patients in the DHBA commenced on 1 January 2018. Patients were considered not eligible for analysis when missing data included date of birth, preoperative imaging modalities used, date of surgery, type of procedure or origin of the tumour for which resection was performed.

No ethical approval was needed as the DHBA is an obligatory audit from the Dutch inspectorate of healthcare and all analyses were performed on an anonymized data set.

Patient groups

In all patients CT of the abdomen and chest was performed as baseline imaging. Patients were divided into four groups for analysis: no additional imaging of the liver; preoperative imaging consisting of CT and ceMRI of the liver; preoperative imaging consisting of CT and ^{18}F-FDG PET–CT; and preoperative imaging consisting of CT, ceMRI and ^{18}F-FDG PET–CT.

Variables

Studied variables included patient characteristics (age, sex, ASA fitness grade, co-morbidity score according to the Charlson Co-morbidity Index (CCI), liver disease before surgery, previous liver surgery for CRLM and year of surgery), tumour characteristics (number of CRLM, diameter of largest CRLM before treatment on preoperative CT, synchronous or metachronous metastases, presence of extrahepatic metastases, and whether metastases were bilobar), and type of hospital and oncological network where treatment took place. Factors contributing to the use of ceMRI, ^{18}F-FDG PET–CT, and combined use of ceMRI and ^{18}F-FDG PET–CT were primary variables for case-mix correction. Other studied variables and parameters were the use of the different preoperative imaging modalities over the years, and between-hospital and between-oncological network variation in the use of preoperative imaging modalities. Both were corrected for case-mix variables.

Table 3 Association model of patient and tumour factors with the use of preoperative [^{18}F]fluorodeoxyglucose PET–CT in patients with colorectal liver metastases in the Netherlands, 2014–2018

	No. of patients (n = 4510)	Univariable analysis*		Multivariable analysis*	
		Odds ratio	*P*	Adjusted odds ratio	*P*
Age (years)			0·314		
≤ 50	315	1·00 (reference)			
50–64	1543	1·13 (0·88, 1·44)	0·333		
65–79	2331	1·22 (0·97, 1·55)	0·096		
≥ 80	314	1·17 (0·86, 1·61)	0·319		
Missing†	7				
Sex			0·622		
M	2831	1·00 (reference)			
F	1679	1·03 (0·91, 1·16)			
Charlson Co-morbidity Index			< 0·001		0·003
0–1	3332	1·00 (reference)		1·00 (reference)	
≥ 2	1125	1·28 (1·12, 1·46)		1·22 (1·05, 1·40)	
Missing†	53				
BMI		1·00 (0·99, 1·02)	0·815		
ASA grade			0·444		
I–II	3589	1·00 (reference)			
≥ III	852	0·94 (0·81, 1·10)			
Missing†	69				
History of liver disease‡			0·156		
No	4321	1·00 (reference)			
Yes	62	0·69 (0·41, 1·15)			
Missing†	127				
History of liver resection			0·132		
No	3662	1·00 (reference)			
Yes	797	1·12 (0·97, 1·31)			
Missing†	51				
History of preoperative chemotherapy			0·044		0·164
No	2842	1·00 (reference)		1·00 (reference)	
Yes	1242	0·87 (0·77, 1·00)		0·97 (0·94, 1·32)	
Missing†	426				
No. of CRLM			0·056		0·235
1	1925	1·00 (reference)		1·00 (reference)	
2	951	0·95 (0·81, 1·11)	0·498	0·89 (0·75, 1·06)	0·170
3	503	1·02 (0·84, 1·24)	0·845	1·04 (0·85, 1·34)	0·786
4	315	0·94 (0·74, 1·19)	0·582	0·96 (0·73, 1·26)	0·561
5	190	0·75 (0·56, 1·02)	0·067	0·80 (0·57, 1·12)	0·206
>5	487	0·75 (0·61, 0·92)	0·005	0·81 (0·64, 1·04)	0·091
Missing†	139				
Maximum diameter of largest CRLM (mm)			0·060		0·018
< 20	1232	1·00 (reference)		1·00 (reference)	
20–34	1510	1·17 (1·02, 1·37)	0·035	1·18 (1·01, 1·39)	0·034
35–54	764	1·28 (1·07, 1·54)	0·007	1·30 (1·08, 1·62)	0·002
≥ 55	478	1·20 (0·97, 1·49)	0·087	1·29 (1·03, 1·62)	0·027
Missing	526	1·21 (0·98, 1·48)	0·072	1·34 (1·06, 1·68)	0·009
Bilobar disease			0·041		0·096
No	2423	1·00 (reference)		1·00 (reference)	
Yes	2043	1·13 (1·01, 1·27)		1·15 (0·97, 1·36)	
Missing†	44				

Table 3 Continued

	No. of patients (n = 4510)	Univariable analysis*		Multivariable analysis*	
		Odds ratio	*P*	Adjusted odds ratio	*P*
Location of primary tumour			0·567		
Colon	2908	1·00 (reference)			
Rectal	1596	0·96 (0·85, 1·09)			
Missing†	6				
Nodal stage of primary tumour			< 0·001		0·104
pN0	1246	1·00 (reference)		1·00 (reference)	
pN1	1194	0·88 (0·75, 1·03)	0·117	0·89 (0·75, 1·05)	0·184
pN2	861	0·93 (0·78, 1·11)	0·429	0·96 (0·80, 0·96)	0·591
Missing	1209	0·66 (0·56, 0·78)	< 0·001	0·80 (0·67, 0·96)	0·024
Type of metastases			< 0·001		< 0·001
Metachronous	2362	1·00 (reference)		1·00 (reference)	
Synchronous	2103	0·66 (0·58, 0·74)		0·66 (0·58, 0·76)	
Missing†	45				
Extrahepatic metastases			< 0·001		< 0·001
No	3823	1·00 (reference)		1·00 (reference)	
Yes	566	1·44 (1·21, 1·73)		1·45 (1·20, 1·75)	
Missing	121				
Type of hospital			0·317		
Regional	2490	1·00 (reference)			
Tertiary referral centre§	2020	0·94 (0·84, 1·06)			

Values in parentheses are 95 per cent confidence intervals. *Multilevel logistic regression model with individuals nested for year of surgery. †Missing values not included in analyses because of relatively small group. ‡Liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis. §Defined as hospitals with highest expertise on oncological surgery.

All variables concerning tumour characteristics were based on normal preoperative work-up before surgery, and therefore assessed using preoperative CT before additional imaging was performed. However, as a result of the retrospective nature of this study, these variables might resemble characteristics of the CRLM after ceMRI or ^{18}F-FDG PET–CT. Sensitivity analyses were performed in all statistical models, which consisted of dropping tumour characteristics.

As described previously[28], oncological networks were classified according to treatment collaboration between hospitals, or topographical location if no collaboration network was present (*Fig. S1*, supporting information). An oncological network consists of one or more tertiary referral centres, including one of the seven university hospitals in the Netherlands. All regional hospitals are included in an oncological network, of which a few perform liver surgery. Regional hospitals not performing liver surgery refer patients to either a regional hospital performing liver surgery or tertiary referral centre for the treatment of CRLM, based on agreements in the oncology network. All hospitals in an oncological network have multidisciplinary meetings using video conferencing to discuss patients with CRLM and obtain a patient-centred treatment plan. If necessary, patients with a high surgical risk as a result of co-morbidity or need for more complex surgical procedures can be referred to tertiary referral centres[28].

Statistical analysis

Baseline characteristics were compared between all groups using the χ^2 test or Fisher's exact test as appropriate for categorical variables. Continuous variables were compared using independent two-samples *t* test.

Identification of case-mix factors, defined as non-modifiable patient and tumour characteristics influencing the use of the different preoperative imaging modalities, was performed. Potential case-mix factors were entered in univariable and multivariable multilevel logistic regression models, one model for each preoperative imaging modality. A multilevel analysis was used to take into account the changes in hospital policy, as well as unmeasured similarities of patients within the year of surgery. Separate analysis for trends in preoperative imaging over the years was performed using univariable and multivariable logistic regression for each treatment modality. These models were performed using case-mix

Table 4 Association model of patient and tumour factors with the use of preoperative contrast-enhanced MRI and [^{18}F]fluorodeoxyglucose PET–CT in patients with colorectal liver metastases in the Netherlands, 2014–2018

	No. of patients (n = 4510)	Univariable analysis*		Multivariable analysis*	
		Odds ratio	*P*	Adjusted odds ratio	*P*
Age (years)			0·289		
≤50	315	1·00 (reference)			
50–64	1543	1·04 (0·80, 1·36)	0·802		
65–79	2331	0·96 (0·74, 1·24)	0·730		
≥80	314	0·80 (0·56, 1·14)	0·218		
Missing†	7				
Sex					
M	2831	1·00 (reference)			
F	1679	1·07 (0·94, 1·23)			
Charlson Co-morbidity Index			0·929		
0–1	3332	1·00 (reference)			
≥2	1125	1·01 (0·87, 1·17)			
Missing†	53				
BMI		1·01 (1·00, 1·03)	0·091	1·01 (0·99, 1·04)	0·204
ASA grade			0·056		0·126
I–II	3589	1·00 (reference)		1·00 (reference)	
≥III	852	0·85 (0·72, 1·00)		0·87 (0·73, 1·04)	
Missing†	69				
History of liver disease‡			0·057		0·057
No	4321	1·00 (reference)		1·00 (reference)	
Yes	62	0·54 (0·27, 1·01)		0·51 (0·26, 1·02)	
Missing†	127				
History of liver resection			0·010		0·760
No	3662	1·00 (reference)		1·00 (reference)	
Yes	797	0·75 (0·64, 0·87)		0·97 (0·81, 1·17)	
Missing†	51				
History of preoperative chemotherapy			0·324		
No	2842	1·00 (reference)			
Yes	1242	1·07 (0·93, 1·24)			
Missing†	426				
No. of CRLM			0·005		0·126
1	1925	1·00 (reference)		1·00 (reference)	
2	951	1·03 (0·86, 1·23)	0·738	0·93 (0·76, 1·13)	0·467
3	503	1·24 (1·00, 1·54)	0·051	1·21 (0·95, 1·55)	0·129
4	315	1·47 (1·14, 1·89)	0·002	1·28 (0·95, 1·71)	0·099
5	190	1·17 (0·84, 1·62)	0·341	1·06 (0·74, 1·53)	0·752
>5	487	1·37 (1·10, 1·69)	0·004	1·22 (0·94, 1·58)	0·140
Missing†	139				
Maximum diameter of largest CRLM (mm)			0·005		0·024
<20	1232	1·00 (reference)		1·00 (reference)	
20–34	1510	0·95 (0·81, 1·12)	0·563	0·95 (0·80, 1·14)	0·615
35–54	764	1·01 (0·83, 1·23)	0·892	1·04 (0·85, 1·28)	0·691
≥55	478	0·98 (0·78, 1·23)	0·854	0·98 (0·77, 1·26)	0·897
Missing	526	0·65 (0·51, 0·83)	<0·001	0·65 (0·50, 0·86)	<0·001
Bilobar disease			0·007		0·107
No	2423	1·00 (reference)		1·00 (reference)	
Yes	2043	1·19 (1·05, 1·36)		1·16 (0·97, 1·39)	
Missing†	44				

Table 4 Continued

	No. of patients ($n = 4510$)	Univariable analysis*		Multivariable analysis*	
		Odds ratio	*P*	Adjusted odds ratio	*P*
Location of primary tumour			0·004		0·005
Colon	2908	1·00 (reference)		1·00 (reference)	
Rectal	1596	1·22 (1·06, 1·39)		1·23 (1·06, 1·42)	
Missing†	6				
Nodal status of primary tumour			0·047		0·016
pN0	1246	1·00 (reference)		1·00 (reference)	
pN1	1194	0·99 (0·83, 1·18)	0·837	0·93 (0·77, 1·12)	0·430
pN2	861	1·08 (0·89, 1·31)	0·421	1·04 (0·86, 1·27)	0·675
Missing	1209	0·83 (0·70, 0·99)	0·043	0·76 (0·63, 0·93)	0·006
Type of metastases			0·155		
Metachronous	2362	1·00 (reference)			
Synchronous	2103	0·91 (0·80, 1·04)			
Missing†	45				
Extrahepatic metastases			0·687		
No	3823	1·00 (reference)			
Yes	566	1·04 (0·86, 1·26)			
Missing	121				
Type of hospital			0·954		
Regional	2490	1·00 (reference)			
Tertiary referral centre§	2020	1·00 (0·88, 1·14)			

Values in parentheses are 95 per cent confidence intervals. *Multilevel logistic regression model with individuals nested for year of surgery. †Missing values not included in analyses because of relatively small group. ‡Liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis. §Defined as hospitals with highest expertise on oncological surgery.

variables to correct for confounding factors associated with the use of the specific preoperative treatment modality.

Case-mix correction was performed using the observed/expected (O/E) ratio, calculated by dividing the observed number of patients who had a preoperative imaging modality by the number of patients expected to receive that modality. The expected number of patients was based on a multivariable multilevel logistic regression model including case-mix variables, resulting in case mix-corrected variability in the use of preoperative imaging modalities between hospitals and oncological networks. An O/E ratio of 1 was considered to indicate that a hospital or oncological network performed exactly the expected amount of preoperative imaging. When the O/E ratio was below 1, a hospital or oncological network performed less preoperative imaging than expected. If the O/E ratio was higher than 1, a hospital or network performed more preoperative imaging than expected. On the basis of the model and O/E ratios for all hospitals or oncological networks, 95 per cent confidence intervals were calculated, indicating statistically significant outliers.

For all multivariable analyses, a two-step method was undertaken. All variables were tested in a univariable model per outcome variable. If a significant association was found ($P < 0·100$, Wald test), the variable was entered in the multivariable model. Statistical significance was defined as a two-sided $P < 0·050$ in the multivariable model. Outcomes were adjusted odds ratios (ORs) and 95 per cent confidence intervals. Multicollinearity was assessed in all multivariable models. This was done by calculation of the variance inflation factor (VIF). A VIF higher than 2·5 was considered to indicate multicollinearity.

All analyses were performed in R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study inclusion period, 4846 patients underwent surgical liver resection for CRLM. Of these, 336 patients were excluded because of missing information on baseline characteristics, preoperative imaging techniques, postoperative outcomes and postoperative oncological classification. A total of 4510 patients were analysed, of whom 1562 (34·6 per cent) had ceMRI, 872 (19·3 per cent) had ^{18}F-FDG PET–CT, and 1293 (28·7 per cent) had both ceMRI and ^{18}F-FDG PET–CT. The remaining 783 patients (17·4 per cent) did not receive any additional imaging apart from CT.

ceMRI or combined ceMRI and ^{18}F-FDG PET–CT was used more often in patients with a history of liver disease, preoperative chemotherapy, synchronous metastases and a rectal primary tumour. ceMRI was used less often in patients with a greater maximum diameter of the largest liver metastases. If more CRLM were present, ceMRI or combined ceMRI and ^{18}F-FDG PET–CT was used more often. In patients with extrahepatic metastases ^{18}F-FDG PET–CT was used more often (*Table 1*).

Factors associated with use of different preoperative imaging modalities

In multivariable multilevel logistic regression analysis, factors positively associated with preoperative use of ceMRI included having an increasing number of CRLM (5 or more tumours *versus* 1 tumour: adjusted odds ratio (OR) 2·45, 95 per cent c.i. 1·89 to 3·17; $P < 0·001$), a rectal primary tumour (adjusted OR 1·44, 1·25 to 1·67; $P < 0·001$) and synchronous metastases (adjusted OR 1·22, 1·05 to 1·41; $P = 0·012$) (*Table 2*). Factors negatively associated with preoperative use of ceMRI included high ASA grade (adjusted OR 0·74, 0·62 to 0·88; $P = 0·001$), history of liver resection (adjusted OR 0·79, 0·66 to 0·94; $P = 0·006$), maximum diameter of the largest CRLM (less than 20 mm *versus* 55 mm or more: adjusted OR 0·32, 0·25 to 0·40; $P < 0·001$), extrahepatic metastases (adjusted OR 0·74, 0·60 to 0·90; $P = 0·003$) and treatment in a tertiary referral centre (adjusted OR 0·79, 0·66 to 0·89; $P < 0·001$) (*Table 2*).

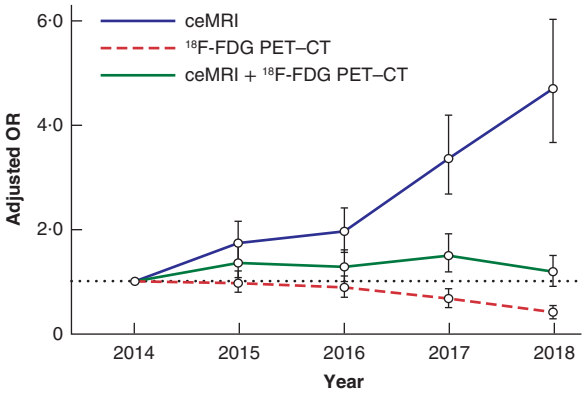
In multivariable multilevel logistic regression analysis, factors positively associated with preoperative use of ^{18}F-FDG PET–CT included higher CCI score (adjusted OR 1·22, 95 per cent c.i. 1·05 to 1·40; $P = 0·003$), maximum diameter of largest CRLM (less than 20 mm *versus* 55 mm or more: adjusted OR 1·29, 1·03 to 1·62; $P = 0·027$) and extrahepatic metastases (adjusted OR 1·45, 1·20 to 1·75; $P < 0·001$) (*Table 3*). Factors negatively associated with preoperative use of ^{18}F-FDG PET CT included only synchronous metastases (adjusted OR 0·66, 0·58 to 0·76; $P < 0·001$) (*Table 3*).

In multivariable multilevel logistic regression analysis, the only factor associated positively with preoperative use of a combination of ceMRI and ^{18}F-FDG PET–CT was rectal primary tumour (adjusted OR 1·23, 95 per cent c.i. 1·06 to 1·42; $P = 0·005$) (*Table 4*). There were no factors associated negatively with the combined use of ceMRI and ^{18}F-FDG PET–CT.

Trends in use of different imaging modalities over the years

In the Netherlands, an increase was observed in the preoperative use of ceMRI, from 9·6 per cent in 2014 to 26·2 per cent in 2018. Univariable and multivariable logistic regression for trend over the years showed that this increase was statistically significant (adjusted OR 4·72, 95 per cent c.i. 3·69 to 6·05; $P < 0·001$) (*Fig. 1*; *Table S1*, supporting information).

Fig. 1 Case mix-corrected trend analysis using multivariable logistic regression for the use of pretreatment imaging modalities for colorectal liver metastases in the Netherlands, 2014–2018

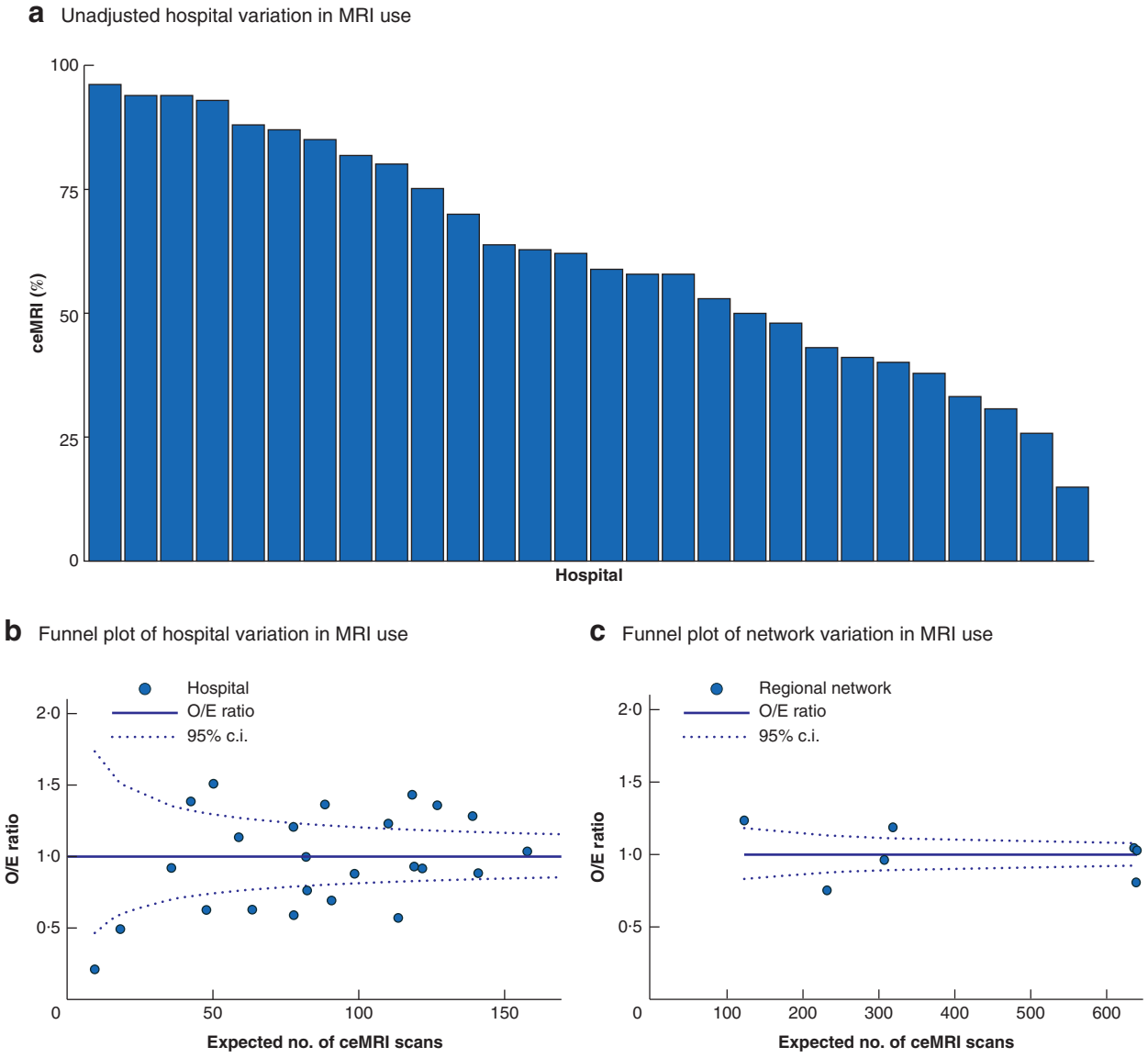


Adjusted odds ratios (ORs) are shown with 95 per cent confidence intervals. Case-mix variables for contrast-enhanced (ce) MRI were age, Charlson Co-morbidity Index (CCI) score, BMI, ASA grade, history of liver resection, number of colorectal liver metastases (CRLM), maximum diameter of largest CRLM, location of primary tumour, type of metastases, extrahepatic metastases and type of hospital. Case-mix variables for [^{18}F]fluorodeoxyglucose (^{18}F-FDG) PET–CT were CCI score, preoperative chemotherapy, number of CRLM, maximum diameter of largest CRLM, bilobar disease, location of primary tumour, nodal status of primary tumour, extrahepatic metastases and type of hospital. Case-mix variables for ceMRI and ^{18}F-FDG PET–CT were ASA grade, BMI, history of liver disease, history of liver resection, number of CRLM, maximum diameter of largest CRLM, bilobar disease, location of primary tumour and nodal status of primary tumour.

The use of preoperative ^{18}F-FDG PET–CT between 2014 and 2016 was stable at around 25 per cent, but use decreased in 2017 (14·7 per cent) and 2018 (6·0 per cent). Univariable and multivariable logistic regression for trend over the years showed that the decreasing trend was statistically significant (adjusted OR 0·42, 95 per cent c.i. 0·29 to 0·54; $P < 0·001$) (*Fig. 1*; *Table S2*, supporting information).

The use of combined preoperative ceMRI and ^{18}F-FDG PET–CT was 15·0 per cent in 2014. During 2015 to 2017 this increased to 24·6 per cent, but was only 16.9 per cent in 2018. Univariable and multivariable logistic regression for trend over the years showed concordant results regarding the use of combined preoperative ceMRI and ^{18}F-FDG PET–CT (*Fig. 1*; *Table S3*, supporting information).

Fig. 2 Unadjusted rates of hospital variation and case mix-corrected funnel plots of between-hospital and oncological network variation in the use of preoperative contrast-enhanced MRI in patients with colorectal liver metastases in the Netherlands, 2014–2018



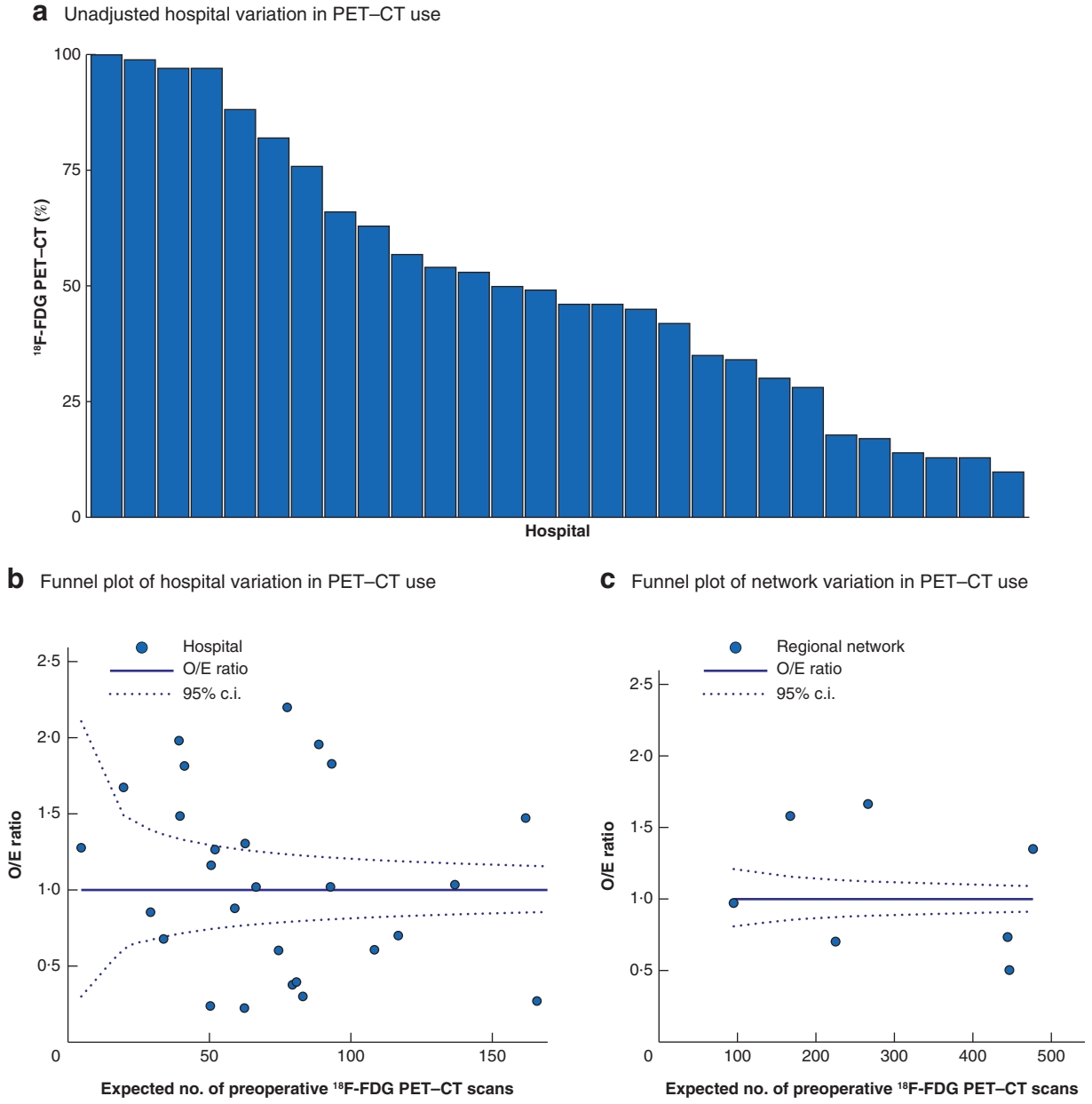
a Unadjusted rates of between-hospital variation in use of contrast-enhanced (ce) MRI. **b** Funnel plot of between-hospital variation, case mix-corrected for age, Charlson Co-morbidity Index (CCI) score, BMI, ASA grade, history of liver resection, number of colorectal liver metastases (CRLM), maximum diameter of largest CRLM, location of primary tumour, type of metastases, extrahepatic metastases and type of hospital. **c** Funnel plot of oncological network variation, case mix-corrected for age, CCI score, BMI, ASA grade, history of liver resection, number of CRLM, maximum diameter of largest CRLM, location of primary tumour, type of metastases, extrahepatic metastases and type of hospital. O/E, observed/expected.

Variation in use of different imaging modalities

Variation between hospitals and oncological networks was present for all preoperative imaging modalities. After case-mix correction, significant hospital and oncological network variation was still present.

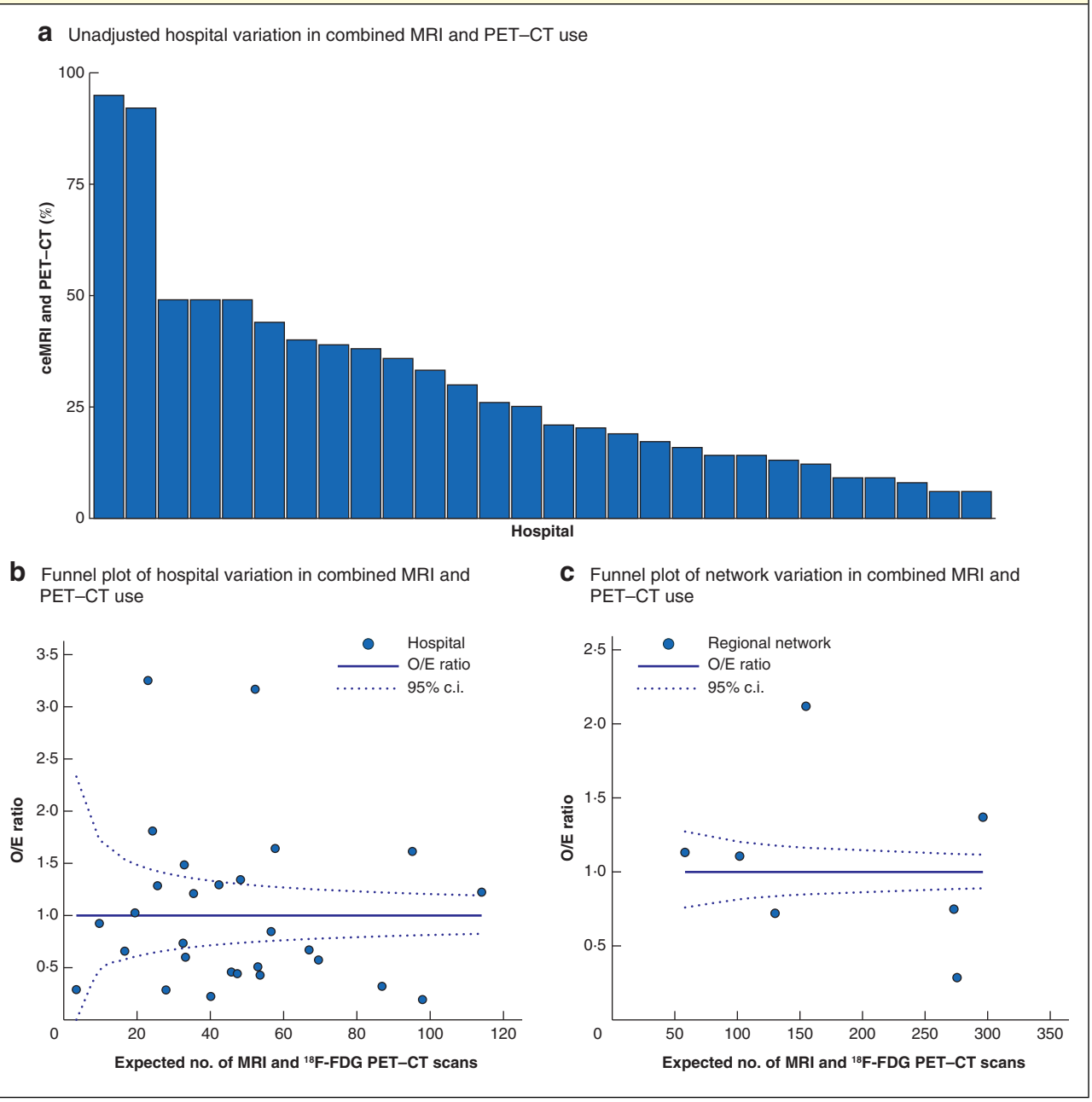
Unadjusted rates for the proportion of patients with CRLM receiving ceMRI in Dutch hospitals ranged between 15.4 and 96.2 per cent (*Fig. 2a*). After case-mix correction, widespread variation was observed in the use of ceMRI in the Netherlands. Seven hospitals performed more and eight hospitals performed less preoperative

Fig. 3 Unadjusted rates of hospital variation and case mix-corrected funnel plots of between-hospital and oncological network variation in the use of preoperative [^{18}F]fluorodeoxyglucose PET–CT in patients with colorectal liver metastases in the Netherlands, 2014–2018



a Unadjusted rates of between-hospital variation in use of [^{18}F]fluorodeoxyglucose (^{18}F-FGD) PET–CT. **b** Funnel plot of between-hospital variation, case mix-corrected for Charlson Co-morbidity Index (CCI) score, preoperative chemotherapy, number of colorectal liver metastases (CRLM), maximum diameter of largest CRLM, bilobar disease, location of primary tumour, nodal status of primary tumour, extrahepatic metastases and type of hospital. **c** Funnel plot of oncological network variation, case mix-corrected for CCI score, preoperative chemotherapy, number of CRLM, maximum diameter of largest CRLM, bilobar disease, location of primary tumour, nodal status of primary tumour, extrahepatic metastases and type of hospital. O/E, observed/expected.

Fig. 4 Unadjusted rates of hospital variation and case mix-corrected funnel plots of between-hospital and oncological network variation in the preoperative use of combined contrast-enhanced MRI and [^{18}F]fluorodeoxyglucose PET–CT in patients with colorectal liver metastases in the Netherlands, 2014–2018



a Unadjusted rates of between-hospital variation in use of combined contrast-enhanced (ce) MRI and [^{18}F]fluorodeoxyglucose (^{18}F-FGD) PET–CT. **b** Funnel plot of between-hospital variation, case mix-corrected for ASA grade, BMI, history of liver disease, history of liver resection, number of colorectal liver metastases (CRLM), maximum diameter of CRLM, bilobar disease, location of primary tumour and nodal status of primary tumour. **c** Funnel plot of oncological network variation, case mix-corrected for ASA grade, BMI, history of liver disease, history of liver resection, number of CRLM, maximum diameter of largest CRLM, bilobar disease, location of primary tumour and nodal status of primary tumour. O/E, observed/expected.

ceMRI than expected based on their case mix (*Fig. 2b*). O/E ratios concerning the use of ceMRI between hospitals ranged from 0·21 to 1·51. In addition, two oncological networks performed more preoperative ceMRI than expected, whereas two other networks performed less preoperative ceMRI than expected, with O/E ratios ranging between 0·75 and 1·23 (*Fig. 2c*).

Unadjusted rates for the proportion of patients with CRLM receiving ^{18}F-FDG PET–CT in Dutch hospitals ranged from 10.0 to 100 per cent (*Fig. 3a*). After case-mix correction, widespread variation in the use of ^{18}F-FDG PET–CT in the Netherlands was observed, with nine hospitals performing more and ten hospitals performing less preoperative ^{18}F-FDG PET–CT than expected based on their case mix (*Fig. 3b*). O/E ratios concerning the use of ^{18}F-FDG PET–CT between hospitals ranged from 0·24 to 2·20. In addition, three oncological networks performed more preoperative ^{18}F-FDG PET–CT than expected and three other networks performed less than expected, with O/E ratios ranging between 0·50 and 1·67 (*Fig. 3c*).

Unadjusted rates for the proportion of patients with CRLM receiving combined ceMRI and ^{18}F-FDG PET–CT in Dutch hospitals ranged between 5.6 and 94.9 per cent (*Fig. 4a*). After case-mix correction, widespread variation in the use of these combined imaging modalities was found. Eight hospitals performed preoperative ceMRI and ^{18}F-FDG PET–CT more often and 11 hospitals performed the combined imaging less often than expected based on their case mix (*Fig. 4b*). O/E ratios for the use of ceMRI and ^{18}F-FDG PET–CT between hospitals ranged from 0·19 to 3·25. In addition, two oncological networks performed preoperative ceMRI and ^{18}F-FDG PET–CT more often than expected, whereas three other networks performed the combined imaging less often than expected, with O/E ratios ranging between 0·29 and 2·12 (*Fig. 4c*).

Multicollinearity was not observed for any of the reported models in this study: the VIF was always below 2·0. Sensitivity analyses, in which tumour characteristics were dropped from the analyses, did not show differences in any of the outcomes.

Discussion

In this nationwide population-based analysis, ceMRI as preoperative imaging for CRLM was used increasingly in the Netherlands over time, whereas the use of ^{18}F-FDG PET–CT decreased. The use of combined ceMRI and ^{18}F-FDG PET–CT remained stable over the years. Use of MRI was associated with smaller diameter of CRLM or more CRLM. Use of ^{18}F-FDG PET–CT was associated with extrahepatic metastases and larger diameters of CRLM. Notable variation was present regarding the use of preoperative ceMRI, ^{18}F-FDG PET–CT, and combined ceMRI and ^{18}F-FDG PET–CT between hospitals and oncological networks in the Netherlands.

Few studies on trends and variation in the use of preoperative imaging have been published in the past. One French study[29] showed that use of preoperative liver ceMRI increased from 53 to 80 per cent between 2009 and 2013, and 72 per cent of patients with resectable CRLM had preoperative ceMRI. In a Swedish population-based study[30], only 2 per cent of all patients with colorectal cancer had preoperative ceMRI of the liver. Unfortunately, this study did not report on trends or report a subanalysis of patients with CRLM.

The available evidence is not conclusive regarding the use of additional preoperative imaging modalities, resulting in variability in the use of ceMRI and ^{18}F-FDG PET–CT. Over the past few years, several studies[8,10,11] have reported superior per lesion detection with MRI compared with conventional CT in patients with CRLM. An earlier report by Rojas Llimpe and colleagues[31] provided insight into the additional value of ceMRI in patients receiving preoperative chemotherapy. Mostly retrospective studies have been performed to assess differences between different types of MRI, such as ceMRI, diffusion-weighted MRI or gadoxetic acid-enhanced liver MRI. New insights into the added value of different types of MRI in a prospective setting are needed. For this reason, the multicentre CAMINO trial (https://www.trialregister.nl/trial/8039): Netherlands Trial Register number NL8039 was commenced in the Netherlands in 2019; this trial aims to provide information concerning the clinical additional value of ceMRI in patients with CRLM.

^{18}F-FDG PET–CT is thought to have lower sensitivity than ceMRI, and is not favoured in the detection of CRLM[4,32]. Detection rates are lower in patients who have received preoperative chemotherapy[32]. One RCT[12] investigated the additional value of ^{18}F-FDG PET–CT in CRLM and concluded that this did not influence survival, whereas several unrandomized studies[15,33,34] indicated that there could be added value for ^{18}F-FDG PET–CT in patients with extrahepatic metastases.

Large randomized trials or prospective multicentre studies on the use of ceMRI or ^{18}F-FDG PET–CT in patients with CRLM have not been conducted, and thus existing guidelines (such as the Dutch guideline) do not provide recommendations on what is needed. The Dutch guideline does not favour either ceMRI or CT in the work-up before liver resection. It advises using ^{18}F-FDG PET–CT only in patients with extrahepatic metastases[22]. In the present study, an increase in the use of ceMRI in

the Netherlands was observed, whereas use of 18F-FDG PET–CT decreased. These trends are probably the result of international publications[4,7,8,10,12,13,15,31,34] reporting the additional value of these imaging modalities.

Interestingly, ceMRI is thought to provide better insight into tumour burden in patients with a medical history of liver disease, and the literature[10,32] indicates that ceMRI could be useful as preoperative imaging in patients undergoing preoperative chemotherapy or who have had previous liver resection. ^{18}F-FDG PET–CT might have added value in patients with a higher nodal status of the colorectal primary tumour. However, this was not the case in the present study, as these factors were not associated with the use of either of the imaging modalities in this population-based cohort. In addition, ceMRI was used less often in tertiary referral centres, whereas there was no difference in the use of ^{18}F-FDG PET–CT in the different types of hospital.

Variation in the use of imaging in the Netherlands could be explained by the fact that the Dutch guideline allows different approaches[35]. Notable variation in imaging at both a hospital and oncological network level reflects lack of consensus on both levels. There are several possible reasons for this. First, there is insufficient evidence and guidelines concerning the use of preoperative imaging in patients with CRLM. Second, health economic discussions could influence the use of these imaging modalities, as ceMRI and ^{18}F-FDG PET–CT are both more expensive than baseline ultrasonography and CT[36]. As there are considerable differences in the costs of the various imaging modalities, it is important to acknowledge these and to assess the cost-effectiveness of imaging modalities for CRLM in the future.

Hospital variation is undesirable from a national healthcare perspective. Either unnecessary imaging was performed or different approaches to imaging led to different patient selection for treatment. It would be interesting to explore whether these differences in preoperative imaging lead to differences in treatment selection, and in disease-free and overall survival. A next step in the audit is to incorporate long-term follow-up to investigate these associations further, to ensure that conclusions can be drawn concerning survival data. The authors advocate clear evidence-based guidelines regarding preoperative imaging for CRLM. This study and the upcoming CAMINO trial can be used to revise the Dutch, and maybe international, guidelines.

The present study has several limitations. First, the disadvantage of the audit data may be accuracy, design and selection of patients. Details including information on the timing of registration of tumour characteristics, multidisciplinary meetings and outcomes of these meetings were missing and could not be retrieved in this retrospective study. The denominator (the sum of patients treated surgically and those treated otherwise) was unclear. Second, it is not mandatory to register open-and-close procedures in the DHBA. This makes it difficult to evaluate the impact of the use of preoperative imaging on perioperative outcomes.

The strength of the study is the nationwide collection of data through mandatory participation of all Dutch hospitals performing liver surgery. Because of the nationwide coverage, the results reflect daily clinical practice. It is possible to reflect on how Dutch clinicians use preoperative imaging and to evaluate hospital and oncological network variation.

Trends over the years show increasing use of ceMRI and decreasing use of ^{18}F-FDG PET–CT for CRLM in the Netherlands. The lack of specific guidelines on preoperative imaging encourages hospital and oncological network variation in the use of ceMRI, ^{18}F-FDG PET–CT, and combined ceMRI and ^{18}F-FDG PET–CT. Convincing evidence concerning effective preoperative imaging modalities for CRLM is needed to decrease nationwide variation.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.